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Caffeic Acid Phenethyl Ester Protect Mice Hepatic Damage Against Cadmium Exposure

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Abstract

The aim of this study is to approach the possible effect and mechanism of caffeic acid phenethyl ester (CAPE) against the toxicity of Cadmium(Cd) on mice liver. Methods: In vivo assays have been performed by evaluating the oxidative damage marker and the antioxidant parameters, meanwhile, the histopathological changes were also observed. Results: It was revealed that the intoxication of Cd could increase the concentration of oxidative damage and decrease the content of antioxidant system, the impact of Cd on liver damage can be suppressed by the effect of CAPE by lowering the oxidative damage levels and improving the activities of antioxidant enzymes. Conclusion: From the data obtained from the studies, we found that the protection effect of CAPE on Cd toxicity was not solely dependent on the antioxidant effect, however, the evidence of CAPE playing a role in the amelioration of Cd toxicity probably showed that CAPE can be a promising agent in the treatment of Cd exposure.

Keywords :cadmium; caffeic acid phenethyl ester; oxidative stress; antioxidant

1. Introduction

Cadmium (Cd) is a heavy metal of increasing prevalence in our environment to which every one is constantly exposed because of its industrial usage and its emission from fuel combustion [1]. Cd has been recognized as one of the most toxic environmental and industrial pollutants and has been classified by the International Agency for Research on Cancer (IARC) as a category I human carcinogen [2]. Once the metal is absorbed, it is retained within the body with little excretion and thus, even in uncontaminated environment or very low concentration, there is an accumulation of the metal within the vital organs,

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causing hepatotoxicity, nephrotoxicity, and cardiomyopathy. Many toxic effects of Cd seem to be indirect and due, at least in part, to oxidative stress owing to the generation of reactive oxygen species (ROS) and the reduction of the main antioxidant compounds in the cells by inactivating enzymes and other antioxidant molecules[3]. Our studies also provided evidences for the toxicity mechanism of Cd [4].

Since natural products have lesser adverse effects than synthetic drugs, there was an upsurge of interest to explore the protective potential of natural products against Cd toxicology. Caffeic acid phenethyl ester (CAPE), identified in propolis (bee glue) from honeybee hives, has been used for many years as a folk medicine [5-7]. CAPE was shown to have potent anti-oxidative effect against carbon tetrachloride-induced liver [8] and kidney injuries in rats [9] and mice [10], and against cisplatin-induced hepatic oxidative damage [11] and improves cellular glutathione (GSH) status. In vitro studies showed that CAPE is effective against experimentally produced liver toxicity [10]. Moreover, the use of CAPE is of less side-effect and without toxicity. Therefore, these advantages of CAPE promote the investigation regarding the potential use of CAPE as a clinical agent against the risk brought by Cd exposure.

Therefore, in vivo experiments were planned, to include oxidative stress indicators (lipid perioxidation(LPO) and protein carboxylation (PCO)), antioxidant defense systems (catalase(CAT), superoxide dismutase (SOD) and GSH) have been designed to test the effect of CAPE against the hepatic damage exposure to Cd. The histopathology of the liver was also evaluated to assess morphological alterations. Our data provide convincing evidences that CAPE can effectively protect against Cd(II)-mediated oxidative damage. Possible interaction of the structure and the protective effect of CAPE have also been discussed. This study may provide some new insights to improve upon and extend the pharmacological utility of CAPE.

2. Results And Discussion

CAPE is one promising agent against various toxicities associated with oxidative stress and peroxidative damage. CAPE was shown to have prominent antioxidant, radical-scavenging and anti-peroxidative activities [5-7]. Herein, the aim of this study was to investigate the protection effect of different concentration of CAPE (0.1, 1, 10uM/kg per day) on mice hepatic damage induced by Cd(II) (1mg/kg per day) via testing the oxidative markers and antioxidant enzymes systems. Moreover, the histopathological parameter has also been evaluated.

As seen in Fig.1, the intoxication of Cd can lead to the decrease of the GSH concentration, revealing the possible involvement of GSH in the toxicological mechanism of Cd, and the treatment of CAPE(10μM/kg) against Cd toxicity significantly normalized tissue GSH level ($p<0.01$), moreover, the effect of CAPE showed a dose-dependent manner, at the dose of 0.1μM/kg , there was no statistic significant between the Cd group and the protection group, providing the evidence that the protection effect is dose-dependent.

The products of lipid peroxidation were recognized as the oxidative marker of Cd-induced tissue damage. The exposure to Cd can lead to a increase in malondialdehyde (MDA) level and this trend was changed by CAPE treatment ($p<0.05$), however, the effects of CAPE showed a dose-independent way, probably involved in the different protection mechanisms of CAPE against the toxicity of Cd, not solely by the antioxidant effect(Fig.2).

On the other hand, histopathological examinations also revealed that CAPE treatment showed some protection on Cd-induced lesions (data not shown)

Results of the current study suggested that oxidative stress along with LPO are important features in Cd-induced hepatotoxicity[3-4]. Although CAPE showed some partial protection on Cd-induced hepatotoxicity, it should be considered that the protective effect of CAPE on Cd hepatotoxicity may not be dependent solely on the antioxidant effect of CAPE. In addition to antioxidant effects, CAPE may also

exert its hepato- protective effect by means of different ways.

According to our previous studies [12], it is suggested that the structural feature responsible for the antioxidative and free radical scavenging activity of CAPE is the ortho-dihydroxyl functionality in the catechol ring. The presence of the electron-donating hydroxyl group at the ortho-position would make the oxidation intermediate and increase the rate of H-atom transfer to peroxyl radicals[13], resulting in the formation of a phenoxy radical. The ortho-hydroxyl phenoxyl radical is more stable due to (1)the unpaired electron can delocalize across the entire molecule [14]; (2) the intramolecular hydrogen bonding interaction as reported recently from both experiments[15] and theoretical calculations[16];(3) ortho-OH phenoxyl radical and/or ortho-semiquinone radical anion shall be easier to further oxidize to form the final product ortho-quinone.

In conclusion, our study provided evidence for the protection effect of CAPE in the prevention of Cd toxicity, probably associated with its antioxidant effect and other effects. Based on this observation, In addition, we also analyzed the potential relationship between the structure and the antioxidant activity of CAPE. Therefore, CAPE and its related folk medicines represent a promising agent for the prevention and treatment of Cd intoxication.

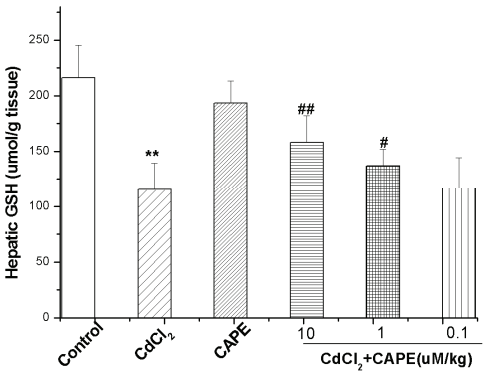

Fig. 1. The effects of CAPE at different concentration on the hepatic GSH level in Cd(II)-exposed mice. Results are expressed as mean ± S.E., n=6-7 animals per group (**p<0.01vs.Control group; **p<0.01, *p<0.05vs.Cd group)

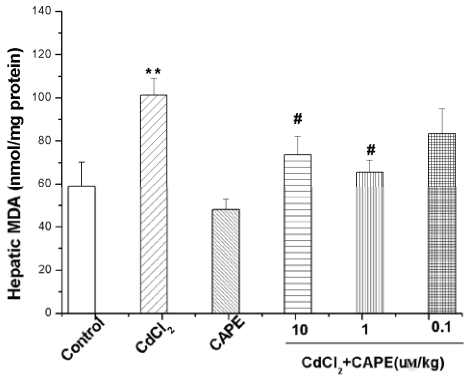

Fig. 2 The effects of CAPE at different concentration on the hepatic MDA level in C d(II)-exposed mice. Results are expressed as mean±S.E.M.; n = 6–7 animals per group (**p<0.01,*p < 0.05 vs. Control group and *p < 0.05 vs. Cd(II) group).

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References

[1] Shaikh ZA, Smith LM. Biological indicators of cadmium exposure and toxicity. *Experientia* 1984;**40**:36–43.

[2] IARC, I.a.f.r.o.c. Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. In: International Agency for Research on Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans, IARC Scientific Publications, Lyon; 1993, 58, p. 119–237.

[3] Nordberg G F. Historical perspectives on cadmium toxicology. *Toxicol and Appl Pharmacol.* 2009; **238**:192–200.

[4] Gong P, Chen FX, Ma GF, Feng Y, Zhao QY, Wang R. Endomorphin 1 effectively protects cadmium chloride-induced hepatic damage in mice. *Toxicology* 2008;**251**:35–44.

[5] Gulcin I. Antioxidant activity of caffeic acid (3,4-dihydrox- ycinnamic acid). *Toxicology* 2006;**217**:213–20.

[6] Russo A, Longo R, Vanella A. Antioxidant activity of propolis: role of caffeic acid phenethyl ester and galangin. *Fitoterapia* 2002;**73**(Suppl. 1):S21–9.

[7] Kart A, Cigremis Y. Caffeic acid phenethyl ester (CAPE) ameliorates cisplatin-induced hepatotoxicity in rabbit. *Exper and Toxicol Pathol* 2010;62(1):45–52.

[8] Kus I, Colakoglu N, Pekmez H, Seckin D, Ogeturk M, Sarsilmaz M. Protective effects of caffeic acid phenethyl ester (CAPE) on carbon tetrachlorideinduced hepatotoxicity in rats. *Acta Histoche,* 2004;**106**:289–97.

[9] Ogeturk M, Kus I, Colakoglu N, Zararsiz I, Ilhan N, Sarsilmaz M. Caffeic acid phenethyl ester protects kidneys against carbon tetrachloride toxicity in rats. *J. Ethnopharmacol* 2005;**97**: 273–80.

[10] Lee KJ, Choi JH, Khanal T, Hwang YP, Chung YC, Jeong HG. Protective effect of caffeic acid phenethyl ester against carbon tetrachloride-induced hepatotoxicity in mice. *Toxicology* 2008;**248**:18–24.

[11] Iraz M, Ozerol E, Gulec M, Tasdemir S, Idiz N, Fadillioglu E, et al. Protective effect of caffeic acid phenethyl ester (CAPE) administration on cisplatin-induced oxidative damage to liver in rat. *Cell Biochem. Func,* 2006; **24**:357–61.

[12] Wu WM, Lu L, Long Y, Wang T, Liu L, Chen Q, et al. Food Chemistry Free radical scavenging and antioxidative activities of caffeic acid phenethyl ester (CAPE) and its related compounds in solution and membranes : A structure – activity insight. *Food Chemistry* 2007;**105**: 107–15.

[13] Lucarini M, Mugnaini V, Pedulli G F. Bond dissociation enthalpies of polyphenols: The importance of cooperative effects". J Org Chem 2002;**67**:928–31.

[14] Graf E. Antioxidant potential of ferulic acid. Free Radical Bio Med, 1992; **13**:435–448.

[15] Chen J H , Ho CT. Antioxidant activities of caffeic acid and its related hydroxycinnamic acid compounds. J Agr Food Chem, 1997;**45**:2374–78.

[16] Wright J S, Johnson ER, DiLabio GA. Predicting the activity of phenolic antioxidants: Theoretical method, analysis of substituent effects, and application to major families of antioxidants. J Am Chem Soc 2001;**123**:1173–1183.